ABSTRACT

Target System

The bacterial phosphotransferase system (PTS) as a drug target system catalyses the uptake and phosphorylation of carbohydrates. It is further involved in signal transduction, *e.g.* catabolite repression, chemotaxis, and allosteric regulation of metabolic enzymes and transporters. It is ubiquitous in bacteria but does not occur in eukaryotes. This uniqueness and the pleiotropic function make the PTS a target for the development of new antimicrobials. Assays are described that lead to the discovery of compounds which uncouple the PTS, by acting as protein histidine/cysteine phosphatases. Uncoupling of the PTS leads to inhibition of carbohydrate transport, repression of catabolite controlled genes (*e.g.* certain virulence genes) and depletion of phosphoenolpyruvate. Compounds from combinatorial libraries with high affinity for phosphoenolpyruvate-protein-phosphatase (Enzyme 1) serve as lead structures for the development of inhibitors and uncouplers of the PTS. Peptides and organic compounds with antimicrobial activities are discovered using these assays. These peptides and organic compounds can be used to inhibit the phosphotransferase system or treat infectious diseases. These peptides and organic compounds can be formulated into pharmaceutical compositions.